1616
JFW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 09/888,126	Confirmation No.: 9053
Applicant	: Jennifer L. Schmitke, Donghao Chen, Richard P. Batycky, David A. Edwards and Jeffrey S. Hrkach	
Filed	: June 22, 2001	
TC/A.U.	: 1616	
Examiner	: Mina Haghighatian	
Docket No.	: 2685.2030-000	
Customer No.	: 000038421	
Title	: Particles for Inhalation Having Rapid Release Properties	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

Sept. 23 2004 (Date) Judy Breen (Signature)

Judy Breen
Typed or printed name of person signing certificate

REQUEST FOR RECONSIDERATION

Sir:

This Request is in response to the Office action of August 11, 2004. No fees are required for this paper.

The Examiner has withdrawn the rejection of the claims over Edwards (US Patent 5,985,309) in view of Patton (US Patent 5,997,848) in favor of a new ground of rejection of all claims over Patton in view of Edwards. Reconsideration is requested.

Patton is relied upon to teach dry powder insulin that can be administered to a mammal, resulting in a systemic delivery characterized by rapid absorption. The

rejection states that the product can be prepared by dissolving insulin in an aqueous buffer (such as a citrate buffer) and spray drying the solution to produce amorphous particles having "a particle size less than 10 microns." According to the rejection, preferred carriers disclosed by Patton include amino acids, such as glycine, lysine, etc. The Examiner notes that insulin and carrier concentrations can be within the broad range of 5-95%, preferably between 20-80% by weight for insulin. The Examiner notes, however, that Patton does not teach the use of DPPC as a carrier.

The Examiner turns to Edwards to establish that surfactants, such as DPPC, are known in the manufacture of insulin-containing inhalation products.

The Examiner suggests that the person of ordinary skill in the art would be motivated to modify the formulations of Patton to use DPPC, as taught by Edwards, because DPPC was known to be a natural lung surfactant. Applicants traverse.

Reviewing the file history of this application, one will see that the first action on the merits dated March 10, 2003 entered a rejection against these claims over Patton in view of Betbeder. In that action, the teachings of Betbeder were relied upon to show that the addition of DPPC to the Patton products was obvious because DPPC was known. That rejection was withdrawn in favor of a rejection over Edwards in view of Patton. In that rejection, the Examiner relied upon Patton to teach the replacement of lactose with citrate buffer. That rejection is now withdrawn, presumably in light of the unexpected results presented in the declaration, to return to a rejection very much like that in the first Office action. In this action, the Examiner now relies upon Edwards, not Betbeder, to teach the addition of DPPC. For many of the reasons offered by Applicants in response to the first and second action, this new ground of rejection should also be withdrawn.

The invention is directed to a very specific formulation consisting of approximately 60% DPPC, 30% insulin and 10% sodium citrate. After the review of a substantial number of formulations, this specific formulation was selected because it had excellent properties. The properties achieved by this specific formulation are not taught by any reference, taken alone or in any combination. The combination of references, whether it is Edwards in view of Patton or Patton in view of Edwards or Patton in view of

Betbeder, simply do not suggest that the selection of these specific components in the specified amounts would achieve the superior properties Applicants have achieved.

The teachings of the references have been disclosed in detail in prior replies. The prior arguments are incorporated by reference and will not be discussed in detail below. Neither Patton nor Edwards teach that the substitution of DPPC for another excipient, such as a sugar or an amino acid, would be expected to result in a rapid release product. Neither Patton nor Edwards provide the motivation to combine the teachings of the reference to arrive at this specific formulation. Indeed, the fact that the Examiner has located in a reference a teaching that DPPC was a known carrier does not satisfy her burden of establishing that it would be obvious to use it in the formulations of Patton. While it is true that substituting equivalent components in a prior art product can raise a *prima facie* case of obviousness, *In re Ruff*, 256 F.2 590 (CCPA 1958), the Examiner has not shown that DPPC and the excipients of Patton are *equivalent*. With respect to environmental stability, these excipients are no more equivalent than, for example, the butter and sugar found in the Examiner's kitchen. Even if it were obvious to use DPPC in a Patton formulation, the reference does not teach the specific amounts of the various excipients. The motivation to combine the teachings of the references must be located in the prior art, not in applicants' disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

As noted in the reply to the first action, one exemplified formulation of Patton includes a formulation which contains about 88% insulin and the balance citrate and citric acid. The stability of the product is not disclosed. A second formulation of Patton contains about 20% insulin, 66% sugar and the balance citrate and citric acid. Again, the stability of the product is not disclosed. To compare the specifically exemplified products of Patton and the claimed invention, the DPPC must, in essence, replace the sugar excipient or about 70% of the insulin. Applicants wish the Examiner to articulate for the record what the person of ordinary skill in the art would expect from such a modification (e.g., insulin compositions with similar properties would be expected to result). This articulation may help to clarify the issue of whether or not an unexpected result was achieved by the Applicants' specific combinations.

Nonetheless, even if the Examiner has established a *prima facie* case of obviousness over the references, taken alone or in any combination, the evidence of record establishes unexpected results.

The Schmitke declaration compares seven formulations. All of the formulations consist of DPPC, sodium citrate buffer and insulin. As such, the formulations compared in the declaration are more relevant than those disclosed by either Patton or Edwards. The declaration compares seven formulations that have 45%, 60%, 75%, 80% and 87% DPPC; 10%, 45% and 3% citrate; and 10%, 15%, and 30% insulin. The 60/10/30 formulation (and 75/10/15 formulation, see copending application USSN 10/179,463) had superior stability in environmental studies. This result could not have been predicted from any of the teachings in the prior art.

The Examiner dismisses the declaration stating that the declaration "primarily shows that formulations containing 10% insulin were not stable... However the primary reference in the new rejection discloses formulations containing 5 to 95% and preferably 20 to 80% insulin." Initially, it is pointed out that the declaration shows more than unstable formulations containing 10% insulin. Formulations that contain 45% and 80% DPPC were not stable, while formulations containing 60% and 75% DPPC were stable. Formulations containing 45% and 3% citrate were not stable while formulations containing 10% citrate were stable. As such, one of ordinary skill in the art would conclude that stability is dependent upon the combination of the components. In any event, the argument is not fully understood.

Perhaps the Examiner is stating that the result is not unexpected in view of the fact that the concentration of insulin in the claims falls within the still broad preferred range of Patton. Patton does not teach that environmental stability would be expected to increase with increased concentrations of protein. Indeed, current insulin products require refrigeration, which would suggest that insulin is not itself generally considered a "stabilizing" component (noting that the kind of stability that the present invention is directed to is not protein stability but maintaining stability of the aerodynamic properties of the formulation). Patton does not teach that DPPC-containing insulin products can possess excellent environmental stability or that the stability of DPPC-containing insulin

products can be superior when the DPPC is present in a 60% concentration. As such, the generic disclosure in Patton that insulin can preferably be added in a concentration between 20 and 80% does not suggest that the data can be ignored or discloses an expected result. Indeed, the court, in *In re Woodruff*, 919 F.2d 1575 (Fed. Cir. 1990), has stated that a *prima facie* case of obviousness based upon overlapping ranges can be rebutted with evidence of an unexpected result.[1]

Perhaps the Examiner is stating that the closest prior art has not been compared since the declaration compares formulations that contain 10% insulin and 30% insulin whereas the reference generically discloses a preferred range between 20 and 80% insulin. The case law does not require an Applicant to compare against the full scope of a preferred or generic range. It need only compare against the closest exemplified product. See, for example, *In re Chapman*, 357 F.2d 418 (CCPA 1966). The Declarant, at her option, can choose to compare an even closer product than that described by the references. *In re Holladay*, 584 G.2d 384 (CCPA 1978).

The Declarant compares formulations which included the recited components of the formulation to establish the criticality of the relative amounts of the components. It is clear that the declaration establishes that not all amounts of insulin, DPPC and buffer behave the same in environmental stability tests. It is believed that this is a closer comparison than a comparison of the impact of the selection of excipients on the formulation *and* the criticality of the concentrations of those excipients. Because of the clear chemical and physical differences between phospholipids, such as DPPC, and amino acids or sugars, such as lactose, raffinose and mannitol, for example, one would not expect environmental studies from one to reasonably extrapolate to other formulations. Thus, even if a 66% raffinose/20% insulin/14% citrate formulation had an inferior environmental stability, the result could not be reasonably extrapolated to a DPPC-containing, raffinose-free formulation. Please recall that even if the prior art formulation had superior properties, the analysis does not change. Patentability is not predicated upon the claimed invention being superior in any or all properties. Rather,

---

[1] It is again noted that the present invention is much more than mere optimization of ranges. It is also a novel combination of components (insulin, DDC and citrate).

patentability can be predicated upon the invention possessing even a single unexpected result. *In re Chupp*, 816 F.2d 643 (Fed. Cir. 1987).

Thus, the declaration compared products closer than those offered in the prior art and established an unexpected result. Nothing more is required and the rejection has been rebutted. Withdrawal of the rejection is requested.

The Examiner has also rejected Claims 1, 3-18, 20-39 and 41-60 under the doctrine of obviousness-type double patenting over copending Serial No. 10/179,463. As noted in the last Office action, the claims of the two applications are no longer overlapping. Further, as established above and in the copending application the relative amounts of components have substantial impact upon the properties of the product. As such, it is believed that the evidence of record rebuts any rejection that can be made. Withdrawal of the rejection is respectfully requested.

Conclusion

In light of the foregoing amendments and remarks, Applicants believe the claims are in condition for allowance and a prompt notice to that effect is requested. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

ELMORE CRAIG, P.C.

By _____
Carolyn S. Elmore
Registration No. 37,567
Telephone: (978) 251-3509
Facsimile: (978) 251-3973

Chelmsford, MA 01863
Dated: 9/23/2004